## REMARKS

Claims 1-74 are canceled.

Claims 75–83 are new claims.

Basis for new claim 75 is submitted to be found in the application as filed in paragraphs [0048] – [0058] of the corresponding patent application publication and in Examples XXXII [0206] and XXXIV [0207].

Basis for new claims 76 is found in [0054].

It is admitted in the Office Action at page 5 that DTT, DHLA and tris(2-CEP) find basis in the application.

It is also admitted in the Office Action at page 7 that claims 77-80 would find basis in the application.

The undersigned has given much thought to the points raised in the Office Action and the new claims presented herein are believed to present the discovery of the inventors in terms that it is hoped will be found acceptable and patentable.

We turn now to the rejections applied to claims 35-41. (now canceled)

We turn now to the rejection under 35 U.S.C. 112, first paragraph, as failing to comply with the description requirement. Broad claim 75 has been drafted to be limited to what the Office Action admits has written description basis; see last four lines of page 4 of the Office Action. Thus the new claims are submitted to meet the description requirement.

We turn now to the rejection under 35 U.S.C. 112, first paragraph, for failing to comply with the enablement requirement.

The Office Action finds enablement for treating angina with the three agents to which claim 75 is limited but finds lack of enablement for the disorders which are recited in claim 36.

Claims 75 and 81-83 have been drafted to eliminate the issue of lack of enablement for certain disorders. These claims are directed to treating a patient who is nitroglycerin tolerant, without reference to disorder for which nitroglycerin was administered to cause tolerance. The invention is more particularly directed to treating nitroglycerin tolerant patient with treating agents that activate inactivated mtALDH. The goal here was to draft a claim commensurate in scope with the invention.

It is noted that it is admitted that enablement is present for patients with angina who are nitroglycerin tolerant. It is submitted that claims 77-80 are therefore admittedly enabled. It is submitted that this admission also constitutes an admission of enablement for treating nitroglycerin tolerant patients. (Claims 75 and 81-83)

Thus claims 75 and 77-83 are submitted to be admitted to be enabled.

We turn now to claim 76.

The Office Action lists as a reason for lack of enablement the contention that nitroglycerin is not useful to treat asthma and relies on Kennedy, T., et al., JAMA 246(2) as evidence of this. This contention is submitted to be irrelevant vis-à-vis claims 75 and 77-83 but in any event is not the whole picture. The Kennedy article is dated July 10,

1981. Since that time others have found nitroglycerin provides a benefit for asthma. See Rolla, G., et al., Pulmonary Pharmacology 1995, April – June, 8(2-3):137-141 and Sharara, A.M., et al., Pulmonary Pharmacology and Therapeutics 11(1), 65-70 (February 1998), copy of abstracts attached.

In view of the rebuttal above, it is submitted that enablement for claim 76 is provided by [0055].

The only other point that seems to have been raised by the 112 lack of enablement rejection is objection to the terms "prevent" and "reverse". These terms are no longer in the claims.

It is submitted that the new claims are therefore free of objection from an enablement standpoint.

Paragraph 7 at page 8 of the rejection mentions a rejection under 35 U.S.C. 112, second paragraph that is maintained. The rejection is not particularized in the current Office Action. The undersigned could not find this rejection in the Office Action of August 14, 2007. In the absence of the examiner on December 17, the undersigned spoke by phone with SPE Hartley who also could not find the rejection. Reconsideration is requested.

We turn now to the prior art rejections.

Claims 35-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Weischer et al. DE 4420 102 A1. The claims require a patient who has received nitroglycerin therapy and has become nitroglycerin tolerant. Weischer et al. fails to

teach administration of DHLA to a patient who has received nitroglycerin therapy and has been become nitroglycerin tolerant. Novelty is present in the new claims in respect to the patient being administered DHLA. The patient of the new claims is not described in Weischer et al. Note further that in Weischer et al. DHLA is administered to provide anti-ischemic effect (see page 2 of the machine translation in Weischer). In other words administration is to negate insufficient oxygen being present. This is a teaching away from the claims herein where administration is to activate an enzyme that has become oxidized. Therefore the claims are also unobvious over Weischer et al.

All the other rejections are under 35 U.S.C. 103(a) and involve Murphy and Laursen. Laursen washes out as indicated at page 7 of the response of September 24. That leaves Murphy which teaches that DTT as a preservative for nitroglycerin caused relaxation when it is initially administered with nitroglycerin. Murphy is defective because it fails to teach DTT will have an effect on a nitroglycerin tolerant patient. The Office Action mentions that the same cascade and effect will inherently be produced in Murphy. The undersigned doesn't understand why this is so. Murphy doesn't teach why DTT preserves relaxation effect of nitroglycerin and Laursen teaches an incorrect reason which would not motivate the claimed invention. The "cascade" effect that the Office Action mentions as being inherent in Murphy is not present in the claimed invention so far as the undersigned can conclude. Without an understanding that inactivated mtALDH is responsible for nitroglycerin tolerance, any effect of DTT in Murphy cannot be considered in the milieu of the new claims. The undersigned

requests that the "cascade effect" referred to in the Office Action be particularized or that a rejection based on Murphy not be implemented against new claims 75-83. Note that DTT was not administered in Murphy in a way to activate inactivated mtALDH in a nitroglycerin tolerant patient since nitrate tolerance was not overcome with DTT in Murphy (see last paragraph, left hand column at page 439 of Murphy) and therefore it is not obvious from Murphy that inactivated mtALDH can be activated by administration of DTT and nitrate tolerance overcome. Withdrawal of the rejections under 35 U.S.C. 103(a) is requested.

This paper is being submitted with a request for continued examination so that the enclosed abstracts will be made of record and the amendments to the claims entered.

Allowance is requested.

Respectfully submitted,
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1: Pulm Pharmacol. 1995 Apr-Jun;8(2-3):137-41.

# Additive effect of nitroglycerine inhalation on beta2-agonist-induced bronchodilatation in asthmatics.

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The current treatment of airway obstruction using beta-agonists and theophylline is designed to increase intracellular level of cAMP. Experimental data show that cGMP and cAMP induce functionally additive relaxation of airways. Nitrates relax smooth muscle through the activation of guanylate cyclase. We wondered whether an additive effect of nitroglycerin (NTG) on beta2-agonist-induced bronchodilatation was present in asthmatic patients. To this aim we evaluated the acute bronchodilating effect of inhaled salbutamol (200 mu g MDI) in 10 asthmatics, pre-treated with inhaled NTG or placebo, in a double-blind cross-over design. FEV1 after NTG was higher than that obtained after placebo (2197 +/- 175 vs. 1981 +/- 155 ml, P <0.001). Mean FEV1 obtained 5 min after salbutamol was higher when patients were pre-treated with NTG than placebo (2694 +/- 217 vs 2440 +/- 228 ml respectively, P <0.001). The bronchodilatation due to salbutamol was identical whether NTG or placebo was inhaled first, respectively at 458 +/- 68 and 497 +/- 44 ml after 5 min. After 15 min FEV1 was higher than baseline, but no significant difference was still present between the value observed after pre-treatment with NTG or placebo (2554 +/- 235 and 2551 +/- 205 ml respectively). In conclusion, in asthmatics nebulized NTG produces a moderate and short-lasting bronchodilatation, which is additive with that produced by salbutamol.

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**Regular Article**

# Nebulized Glyceryl Trinitrate Exerts Acute Bronchodilator Effects in Patients with Acute Bronchial Asthma*[1]

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## Abstract

Glyceryl trinitrate (GTN) is a potent smooth muscle relaxant and vasodilator. There are conflicting reports regarding its efficacy as a bronchodilator. The aim of this study was to examine whether nebulized GTN has bronchodilating effects in patients with acute bronchial asthma. We studied 18 patients (five female, 13 male) who were admitted to the hospital with acute severe asthma on two occasions, administering either 6 mg nebulized GTN or placebo (saline) in a double-blind, randomized, crossover fashion. Bronchial response was assessed by measurement of peak expiratory flow (PEF), forced expiratory volume in 1 s ($FEV_1$) and forced vital capacity (FVC). A systematic effect of this dose of GTN was demonstrated by a mean increase in heart rate of 38.1% (SEM=7.6%) after GTN administration from supine to erect posture, compared with 10.2% (SEM=1.8%) after placebo ($P$<0.005). Systolic blood pressure decreased by 8.7% (SEM=1.1%) after GTN, compared with 4.0% (SEM=2.1%) after placebo ($P$<0.05). Diastolic blood pressure did

not change significantly. Baseline PEF, $FEV_1$ and FVC did not differ on the two experimental days; however, acute bronchodilating effects were seen: PEF (l/min); 368 (21) pre-GTN, 411 (22) post-GTN and 384 (23) post-placebo ($P<0.001$). $FEV_1$ (l); 2.12 (0.13) pre-GTN, 2.46 (0.15) post-GTN and 2.25 (0.16) post-placebo ($P<0.001$). FVC (l); 3.31 (0.17) pre-GTN, 3.75 (0.2) post-GTN and 3.54 (0.2) post-placebo ($P<0.001$). In conclusions, nebulized GTN has bronchodilating effects in patients with acute bronchial asthma. The exact mechanism of bronchodilation is not known, but it may be due to local effect on bronchial smooth muscles through nitric oxide or by systemic vasodilatation which leads to a decrease in pulmonary artery pressure and pulmonary vascular resistance, or an increase in systemic catecholamine release.



**Author Keywords:** Glyceryl trinitrate, Bronchodilator, Inhalation, Salbutamol, Asthma.

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